Rabbit Analgesia

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KEYWORDS

- Rabbit • Analgesia • Pain assessment • Opioid
- Nonsteroidal anti-inflammatory drugs

Rabbits are a very common household pet in the United States, with an estimated 6 million pet rabbits in 2007, an increase of almost 30% from 2001.[1] With increasing popularity, the complexity of diagnostic and surgical procedures performed on rabbits is increasing, along with the frequency of routine surgical procedures. More practitioners are faced with the need to provide adequate analgesia for this species. Pain is probably undertreated in animals in general and, at least in some parts of the world, it is less common to administer analgesics to rabbits as compared with dogs and cats.[2,3] Reasons for this may include less familiarity with the species, smaller knowledge base regarding analgesic dose, efficacy and safety in rabbits, concerns over possible side effects of some analgesics in rabbits, and the difficulties in assessing pain, and efficacy of pain management, in rabbits. While some of these concerns are valid, the underlying physiologic and anatomic similarities of all mammals would suggest that rabbits experience pain, like other more familiar mammalian species, and thus we are ethically obliged to provide relief to those animals in situations where it is likely they would experience pain such as trauma, surgery, and disease.

Untreated pain has many undesirable effects such as activation of complement cascade, cytokine systems, and arachidonic acid cascade, in addition to activation of the sympathetic nervous system. Sympathetic nervous system activation may result in tachycardia, arrhythmias, vasoconstriction, altered cardiac output, and increased myocardial oxygen demand. Alterations in organ perfusion, fluid, electrolyte, and acid-base balance may occur. Pain may alter respiratory rate and reduce tidal volume, which may intensify any existing respiratory compromise. Other detrimental effects of untreated pain include inducing a catabolic state, reduced appetite or anorexia, delayed wound healing, lowered immune responses, and prolonged hospital stays. Pain can also reduce gastrointestinal motility. Concurrent reductions in food intake, dehydration, and disease processes such as enterotoxemia and hepatic lipidosis, could all further promote ileus and may induce life-threatening problems in the rabbit. Critically ill or traumatized patients have the fewest physiologic reserves to deal with these additional insults. Untreated pain increases morbidity

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and potentially increases mortality in many species, and maybe more so in a prey species like the rabbit. In the extreme, there are anecdotal reports of painful rabbits going into shock and dying despite their underlying illness or injury not appearing to have been life-threatening.

Understanding the physiology of pain is essential in the ability to prevent or alleviate pain. In simple terms, the pain pathway begins with detection of a noxious stimulus by the nervous system (transduction). This information is then relayed to the central nervous system (transmission) where information is integrated and processed and in turn relayed to higher centers, where it is interpreted as pain (perception). Analgesic drugs target the pain pathways at one or more of the aforementioned steps (multimodal analgesia). Untreated pain can increase the sensitivity of both the peripheral and central nervous system to stimuli, both painful and not traditionally considered painful, increasing the pain experienced by the animal or even creating scenarios whereby nonpainful stimuli, like touch, are painful to the animal. Persistent untreated pain may result in nervous system damage and the development of neuropathic pain. Although the evidence for such conditions in animals is sparse, neuropathic pain syndromes are being increasingly recognized in veterinary medicine.[4–6] Providing analgesia before application of the painful stimulus (preemptive analgesia prior to planned surgical interventions) may reduce nervous system changes in response to noxious input, as well as reduce postoperative pain levels and analgesic drug requirements. It is more difficult to control established pain. Perception is abolished by general anesthesia because those drugs produce unconsciousness, but many general anesthetics do not inhibit processing of noxious stimuli by the peripheral nervous system or spinal cord, and so do not prevent these aforementioned nervous system changes (sensitization). Concurrent administration of analgesic drugs to anesthetized patients undergoing painful procedures is warranted both pre- and intraoperatively as well as postoperatively. Heightened perception, for example by fear and/or anxiety, will likely increase pain perception and should be avoided. Pharmacologic treatment of pain is only part of a global pain management plan that also considers appropriate housing, husbandry, nursing care, physical therapy, and alternative therapeutic modalities such as acupuncture.

RECOGNIZING PAIN IN RABBITS

Recognizing pain in any species can be challenging but particularly so in the rabbit. There are no generally accepted objective criteria for assessing the degree of pain experienced by a rabbit, and individuals can vary greatly in their response to painful stimuli. In other companion species, behavior-based pain scoring systems have been developed and implemented with success in clinical practice.[7,8] Behavior-based pain assessment schemes are those that include assessment of behaviors and interaction with the animal. Attempts have been made to develop such systems in rabbits but with little success, due to the effects of the observer on animal behavior.[9] There are also several contributory factors. As a prey species, rabbits evolved to hide weaknesses to avoid predation, and as such they may hide their pain to keep a normal appearance when directly observed by strangers. Normal rabbits are bright, alert, active, and very inquisitive; however, an anxious or scared rabbit will freeze and thus its behavior is not assessable. Clinically, rabbits often appear to respond to pain or distress by remaining motionless and so have little activity or behavior to be assessed. To exhibit normal behavior it is important that rabbits be housed in an environment in which they feel safe. In addition, behavioral observations by strangers may need to be made indirectly through a viewing panel or camera in order for the animals to behave freely.[10] Behavioral observations are best made by individuals with detailed knowledge of normal rabbit behavior in given situations, and ideally the behavior of the individual rabbit.

Alterations in heart rate, respiratory rate, and blood pressure may be consistent with pain but these can also be caused by a variety of other factors. These parameters are under complex physiologic control and may be altered by pharmacologic agents, disease processes, stress, and anxiety (and it is likely that any hospitalized, sick, or injured rabbit will be anxious). Restraint has been shown to alter physiologic parameters such as respiratory and heart rate.[11] Changes in heart rate and respiratory rate in dogs have been shown not to correlate with pain scores.[12] More sophisticated evaluation of heart rate variability may be more indicative of pain; however, this is not within the realms of clinical medicine at this time.[13,14]

Animals in pain frequently reduce their food and water intake, or stop eating and drinking altogether, resulting in weight loss and anorexia associated with gastrointestinal problems. Appetite and weight changes have been used as indicators of pain.[15–17] In laboratory rabbits after ovariohysterectomy, food and water consumption was reduced for 2 to 3 days after surgery and was associated with significant reduction in body weight.[10] Although the evidence is consistent that pain reduces food and water intake, pain is not the only potential cause and therefore these signs are not specific. In addition, such changes are typically only apparent in retrospect, and may not be useful in assessing an animal in acute pain.

Behavioral indicators of pain include changes in posture, locomotion, or gait. Posture is altered to avoid moving or contacting painful areas of the body (guarding) and locomotor activity is reduced overall.[18] In laboratory studies, rabbits with acute foot pain had sudden movements and vocalizing, followed by limping, abnormal posture, and licking of the affected area.[19] In these group-housed animals, both social and motor activity of the affected animals was significantly reduced. Of note, the behavior of the entire group was affected by pain in the dominant member of the group. Pain in a member of a group of rabbits may be one factor to evaluate if changes in group dynamics occur.

The effect of pain on activity levels may also depend on the time of day and the intensity of the stimulus.[20] Acclimatized laboratory rabbits were videotaped pre- and post-ovariohysterectomy, and their behavior analyzed to compile several behaviors that may be useful indicators of pain in rabbits.[10] In this study "inactive pain behavior" was considered the most useful indicator of pain, as it was observed either not at all or very infrequently preoperatively, and very frequently postoperatively. In further support of such behaviors as indicators of pain, they decreased in frequency during each of the 4 postoperative days. Inactive pain behaviors consisted of twitching (rapid fur movement on the back), wincing (rapid backward movement associated with eye closing and swallowing), staggering (partial loss of balance), flinching (rapid upward body jerks for no reason), pressing (pushing abdomen toward floor), very slow postural adjustments, and shuffling (walking at very slow pace).

In the aforementioned study, behaviors that indicate activity (movement, searching, interaction, rearing, standing, grooming, and exploring) decreased, and behaviors that indicate inactivity (no-behavior, lying down) increased immediately postoperatively compared with preoperative values, and did not return to baseline for 3 days.[10] Activity behaviors, either reduced activity or increased inactivity, may be challenging to use for assessment of pain in rabbits because there is considerable variation between individuals and it requires long periods of indirect observation. In addition, in the ovariohysterectomy study rabbits were significantly more active in the afternoon than in the morning, and there was considerable variation between individuals.[10] Moreover, long periods and indirect observation are required to assess changes in the duration of those behaviors. Other problems with using activity type behaviors are considering how those behaviors will be affected by drugs, for example, sedation or anesthetic recovery, or disease (systemic debilitation) that may preclude the animal from moving or exploring and yet not always be associated with pain.

NONPHARMACOLOGIC CONSIDERATIONS FOR PAIN MANAGEMENT

Factors other than drug therapy should not be overlooked in pain management in rabbits. Gentle tissue handling and good surgical technique will reduce the degree of postoperative pain. While hospitalized, rabbits should be provided with appropriate housing that is away from the sight, smell, and sound of predatory species. The area should be quiet and the animals kept clean and dry. Attention should be paid to making sure animals have easy access to food and water, particularly if they have mobility issues. Appropriate nursing care by attending to wounds, bandages, urination, and defecation will also help to improve patient comfort. Animals should be handled carefully and restrained appropriately to avoid unnecessary stress. Some animals that are normally housed with another rabbit may find the social isolation stressful, and consideration should be given to bringing their “buddy” rabbit into hospital with them.

PHARMACOLOGIC PAIN MANAGEMENT

Acute pain can occur following surgical procedures, trauma, and a variety of medical conditions, particularly those associated with an inflammatory component. To create an analgesic plan it is helpful to consider the pain severity, likely duration, whether the animal will be hospitalized, and the level of monitoring and care available. Drugs can then be selected to address those criteria in conjunction with factors such as underlying medical or physiologic conditions that may increase an animal’s susceptibility to side effects of some classes of drugs.

There are 5 main classes of drugs used for acute pain management: opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, $\alpha 2$-agonists, and miscellaneous (eg, *N*-methyl-D-aspartate [NMDA] receptor antagonists, serotonin reuptake inhibitors, calcium channel antagonists). There is comparatively little experimental work published on analgesics in rabbits. Most of the drugs and doses used in practice today are based on extrapolation from other species and clinical experience. Suggested doses and routes of administration of analgesic drugs for use in the rabbit are listed in **Table 1**.

Opioids

Opioids are the mainstay for management of moderate to severe pain. Opioids produce analgesia by binding to mu and/or kappa opioid receptors. These receptors are found within the central nervous system, where they exert antinociceptive effects by inhibiting ascending nociceptive input, activating descending inhibitory pathways, and decreasing neurotransmitter release.[21] A growing body of work suggests that opioids may also act peripherally in inflamed tissues.[22] These drugs can be administered systemically, orally, locally (eg, intra-articular), and via the epidural or subarachnoid route. Significant opioid side effects in mammals include sedation, respiratory depression, and reduced gastrointestinal motility. The inhibition of gastrointestinal peristalsis is due to activation of mu and/or kappa opioid receptors expressed by enteric neurons and intestinal muscle cells.[23] Both mu and kappa opioid receptor agonists have been shown experimentally to inhibit motility in the isolated rabbit

Table 1
Suggested systemic analgesic drugs and dosages for use in rabbits[a]

Drug	Dose (mg/kg)	Route	Interval (hours)	References	Comments
Opioids					
Buprenorphine	0.02–0.1	SQ, IM, IV	6	[27]	Reported duration of effect variable and may be dose dependent, clinical duration may only be 4–6 h
Butorphanol	0.1–0.5	SQ, IM, IV	2	[27,28]	Duration of effect may be dose dependent
Morphine	2.0–5.0	SQ, IM	3–4	[31]	
	0.1	Epidurally		[a]	
Oxymorphone	0.1–0.3	SQ, IM, IV	3–4	[a]	
Tramadol	10	PO	12–24	[a]	Pharmacokinetic data reported to be variable, data on clinical efficacy lacking
NSAIDs					
Carprofen	4.0	SQ	24	[a]	
	2.0–4.0	PO	12–24	[a]	
Meloxicam	0.3–0.5	SQ	24	[a]	
	0.5–1.5	PO	24	[10,38]	

Abbreviations: IM, intramuscular; IV, intravenous; PO, per os (orally); SQ, subcutaneous.

[a] Recommendation based on personal experience and anecdotal reports.

intestine.[24,25] Morphine administered intrathecally to rabbits has been shown to suppress duodenal peristalsis.[26]

The analgesic efficacy of systemically administered opioids has been evaluated in some experimental models of pain in rabbits. Buprenorphine, butorphanol, nalbuphine, and pentazocine all increased skin twitch latency in response to focused laser applied to the shaved dorsum of experimental rabbits.[27] In that study, increasing doses of buprenorphine from 0.0075 mg/kg to 0.3 mg/kg appeared to have little effect on maximum analgesia (as assessed by prolongation of skin twitch), but did increase duration of effects from an average of 150 minutes at the lowest dose to greater than 780 minutes at the highest dose. This finding is consistent with the agonist-antagonist (eg, butorphanol) or partial-agonist opioids (buprenorphine) displaying a “ceiling effect” in the magnitude of analgesia they provide.[21] Due to this ceiling effect, opioids of this category are suitable for the treatment of mild to moderate pain. In addition, the half-life of butorphanol in the rabbit is short, and duration of effect is limited to 2 to 3 hours at maximum.[27,28]

Buprenorphine is one of the most commonly used opioids in rabbits because of to its long duration of effect, as well as its partial-agonist activity and assumed lower incidence of side effects compared with mu-agonist opioids. Experimental evidence to support this is limited. Buprenorphine has been documented to reduce respiratory rate, slightly increase arterial pCO_2 levels, and produce mild hypoxemia in awake healthy rabbits at a dose of 0.016 to 0.02 mg/kg administered intravenously.[29] Despite limited experimental evidence suggesting a duration of effects of over 12 hours, clinically the duration of analgesic provided by buprenorphine is variable and may last only up to 6 hours.[27]

Buprenorphine should be reserved for the management of mild to moderate pain that is not expected to change in severity. First, due to its limited analgesic potency, increasing doses are not likely to increase the magnitude of analgesia. The behavioral signs of pain associated with experimental myoma viral infection were not abrogated by buprenorphine at 0.03 mg/kg every 12 hours.[30] Second, buprenorphine has a high affinity for mu opioid receptors and, as such, is hard to displace from those receptors, either by an antagonist if reversal is desired or by a pure agonist if more potent analgesia is required.

Mu opioid receptor agonists are the most effective therapy for acute pain, providing rapid-onset, dose-dependent analgesia. Morphine has been shown to be an effective analgesic in rabbits in a thermal stimulus based experimental model.[31] Other mu-agonists such as oxymorphone and hydromorphone have been reported anecdotally to be effective analgesics in rabbits, with fewer side effects than morphine. In many species, there is marked individual variation in dose requirements, side effects, and tolerance to opioids of the same class; this is likely also true in rabbits. Although rabbits should be monitored for undesirable effects of opioids, pain in itself can also result in respiratory depression, abnormal behavior, depressed food intake, and ileus. Concern regarding those effects should not result in the withholding of adequate analgesia to painful rabbits. Opioid-associated ileus needs to be identified early, and managed by syringe feeding and by maintaining adequate hydration.

Opioids may cause sedation in rabbits. Whereas buprenorphine does not cause obvious reduction in activity levels in healthy rabbits, butorphanol and the mu-agonist opioids can cause marked reductions in activity levels and moderate to marked sedation, particularly at high doses.[27,31] The magnitude of sedation or inactivity produced by opioids may be affected by systemic health of the individual rabbit and its level of pain, and these factors should be considered when evaluating the therapeutic efficacy.

Fentanyl is a potent mu opioid receptor agonist with short duration of action, used commonly in combination with fluanisone as an anesthetic premedicant in rabbits in some parts of the world.[32,33] In other species fentanyl is most commonly used as an infusion during anesthesia or in the immediate postoperative period to provide titratable, potent analgesia. Fentanyl constant-rate infusions have been used intraoperatively to provide analgesia to rabbits and subjectively allow lowering of anesthetic vaporizer settings. However, respiratory depression at higher doses can be marked, necessitating positive pressure ventilation. Dose requirements, efficacy, anesthetic sparing, and hemodynamic effects vary between species and have not been reported in rabbits.

Transdermally delivered fentanyl results in variable plasma levels in rabbits.[34] In some rabbits rapid hair regrowth in the patch application area was thought to significantly inhibit drug absorption. Twelve to 24 hours after application of a 25 μg/h patch, average plasma fentanyl concentrations ranged from 0.5 to 1.5 ng/mL and remained there until patch removal at 72 hours. Interindividual variation was marked and, although those plasma levels would be considered therapeutic in people, the therapeutic plasma fentanyl concentration required for analgesia in the rabbit is not known.

Morphine, due to its intermediate lipid solubility, is well suited for epidural administration. Onset of effect is slow (up to 1 hour); however, systemic uptake is limited and the duration of effect is long (up to 20 hours in some species). Epidural administration of preservative-free morphine may be useful for perioperative analgesia in rabbits undergoing orthopedic surgery or extensive surgery of the abdominal or thoracic cavities, with minimal systemic effects and no motor blockade. The lumbosacral epidural injection technique in rabbits is similar to that described for other small animal species, with the exceptions of the interarcuate ligament not being very deep and a distinct "pop" not often being perceived when passing through it.[35] The rabbit spinal cord terminates within the sacral vertebrae, typically at the level of S2.[36] The incidence of subarachnoid puncture is relatively high in rabbits when epidural puncture is attempted, because of these anatomic features. In such circumstances cerebrospinal fluid either appears in the hub of the needle or can be aspirated. One-third to one-half of the drug dose and volume calculated for epidural administration can be administered into the subarachnoid space.

Nonsteroidal Anti-Inflammatory Drugs

As a group, these drugs have anti-inflammatory, analgesic, and antipyretic activity, and are useful for management of mild to moderate acute or chronic pain, particularly if there is an inflammatory component.[37] These agents appear to act synergistically with opioids, such that lower doses of opioids can be used in combination with NSAIDs. Onset of action of NSAIDs is relatively slow and the dosing interval relatively long. Oral NSAIDs are particularly useful for extending postoperative pain control for several days and in managing chronically painful conditions. These drugs have well known side effects in other species including renal dysfunction, hepatic dysfunction, gastrointestinal ulceration, and inhibition of platelet function. Although theoretically these drugs would seem to be most beneficial when administered before tissue injury, their use preoperatively remains controversial due to their potential for harm. Even healthy rabbits are frequently hypotensive under general anesthesia, which may increase the risk for development of side effects from these drugs. The clinical significance of this has not been well investigated in the rabbit.

NSAIDs have been used extensively in rabbits, although there is little published information. The pharmacokinetics of orally administered meloxicam, a cyclooxygenase-2 preferential NSAID, has been reported.[38] In this study significant interindividual variability in absorption and clearance was reported. There were no obvious adverse clinical effects, changes in serum biochemistry, or deviations in normal weight gain in healthy New Zealand white rabbits after daily administration of 1.5 mg/kg for 5 days. Oral administration of meloxicam is well tolerated by rabbits.[10,38] Meloxicam per os at 1 mg/kg post surgery followed by 0.5 mg/kg once daily for the 2 following days caused a significant reduction in some pain-associated behaviors associated with ovariohysterectomy.[10] Due to the side effect profile of NSAIDs in other species, consideration should be given to monitoring rabbits receiving chronic NSAID therapy with serum biochemistry profiles and fecal occult blood tests.

Local Anesthetics

Local anesthetics, such as lidocaine and bupivacaine, are used commonly in veterinary medicine to reversibly inhibit neural transmission. Local anesthetics can be applied topically, via infiltration, administered intra-articularly, by regional nerve block, or by epidural or subarachnoid injection. Analgesia to the desensitized area is complete and, by abolishing neural input to the central nervous system, the immediate central sensitization induced by noxious stimulation is reduced. Local anesthetic techniques can be useful in conjunction with general anesthesia to provide analgesia, reduce the required anesthetic dose, and reduce postoperative analgesic requirements.

Incisional line blocks and wound infiltration are simple, cost-effective means to provide analgesia that are underutilized in small animal medicine. Doses of 2 mg/kg lidocaine and 1 mg/kg bupivacaine would be suitable for such purposes. Specific nerve blocks may be particularly useful to facilitate dental procedures in rabbits. Directions for performing infraorbital, mental, mandibular, and maxillary nerve blocks have been described in the rabbit.[39]

Epidural or subarachnoid administration of local anesthetic can be performed in the rabbit, resulting in complete sensory and mild to severe motor impairment to the hind limbs. Epidural administration of 0.2 mL/kg of 2% lidocaine results in rapid-onset (1–3 minutes) sensory and motor block to the hind-quarters of approximately 30 to 40 minutes' duration in rabbits.[40] Bupivacaine is longer lasting and, if used at lower concentrations, may produce a more discriminative block, providing longer epidural analgesia with minimal motor effects. Bupivacaine has not been well investigated in rabbits. In practical terms, hind-limb motor blockade in nonanesthetized rabbits may cause them severe distress and lead to self-induced injury. Considerations and side effects of epidural or subarachnoid local anesthetics are the same as those in other species.

Intravenous infusion of lidocaine has become popular recently for provision of analgesia and as a gastrointestinal promotility agent in other species. The clinical use of lidocaine for this purpose has not been investigated in the rabbit. In the cat, lidocaine infusion has a significant negative impact on the cardiovascular system[41]; however, there is some evidence to suggest that this is not the case in rabbits.[42] Further investigations on efficacy and safety are warranted before lidocaine infusions can be recommended for analgesia in rabbits.

Local anesthetics have dose-related toxic side effects on both the central nervous system and the cardiovascular system. Care should be taken to avoid administration of toxic doses of local anesthetics in small patients such as rabbits. Although not well documented, doses of bupivacaine and lidocaine below 2 and 4 mg/kg, respectively, for infiltration or regional block, should avoid toxicosis.

α2-Adrenergic Agonists

The α2-adrenergic agonists possess sedative, muscle relaxant, sympatholytic, and analgesic properties, and are reversible. Used pre- or intraoperatively they can also dramatically reduce anesthetic requirements.[43] These drugs have a marked impact on the cardiovascular system, reducing heart rate and cardiac output. Their use should be reserved for clinically healthy patients. "Microdose" medetomidine has been suggested to avoid the negative cardiovascular effects of these drugs, and although the magnitude of cardiovascular depression is dose dependent, even small doses produce clinically relevant reductions in cardiac output. In the dog, 1 μg/kg reduced cardiac index by greater than 50% of baseline,[44] and constant-rate infusions of 1, 2, and 3 μg/kg/h reduced cardiac index by 50%, 65%, and 70%, respectively, from baseline.[45]

Miscellaneous Drugs

The NMDA receptor antagonist ketamine is used commonly in rabbits for heavy sedation to anesthesia. The NMDA receptor has a significant role in the development of central sensitization. NMDA receptor antagonism may reduce this phenomenon and thus reduce postoperative analgesic requirements.[46] Ketamine infusions have been suggested in veterinary patients as having anesthetic-sparing and antihyperalgesic effects; however, these have not been studied in rabbits. NMDA receptor antagonists have also been used with some success in rodent models of chronic pain.[47] The psychomimetic, sedative, and motor effects of higher doses of ketamine limit its use for such purposes; however, other NMDA receptor antagonists devoid of those properties may be useful. Clinically, chronic pain syndromes have not been well recognized to date in the rabbit; however, as our understanding and ability to recognize pain in rabbits increases, such syndromes are likely to become apparent.

Tramadol is an analgesic with multiple mechanisms of action. Tramadol has some activity as a mu opioid receptor agonist; it also has serotonin and norepinephrine reuptake inhibitory activity and α2-adrenergic agonist activity.[21] The pharmacokinetics of tramadol have been described in the rabbit after both oral and intravenous administration.[48,49] Intravenous administration of tramadol in isoflurane-anesthetized rabbits resulted in widely variable plasma levels of tramadol and its M1 metabolite.[50] After oral administration of 11 mg/kg of tramadol, plasma concentration of tramadol and its active metabolite *O*-desmethyltramadol (M1) were variable and below those levels considered analgesic in people.[49] Therapeutic plasma levels in the rabbit are not known, and the effective dose and dosing interval have not been established in rabbits. Tramadol anecdotally has been used in the clinical management of chronic pain in rabbits; however, palatability appears to be an issue when compounding the drug for use in rabbits.

SUMMARY

Due to their evolution as a prey species, rabbits are reluctant to demonstrate abnormal behavior in the presence of an observer and as such are a challenging species in which to identify pain. Creation of a rabbit-friendly environment within the veterinary hospital in conjunction with remote observation will facilitate detection of behaviors commonly associated with pain, such as reduced activity, reduced motility, abnormal posture, wincing, flinching, abdominal pressing, and staggering. An effective analgesic plan has both pharmacologic and nonpharmacologic components. Analgesic therapy should target multiple locations within the pain pathway, and is an integral part of the management of surgical and trauma patients as well as acute and chronic medical conditions in the rabbit. Many analgesics are associated with side effects; however, with careful dosing and monitoring these are unlikely to be as detrimental to the patient as untreated pain.

REFERENCES

1. American Veterinary Medical Association. U.S. Pet Ownership & Demographics Sourcebook (2007 Edition). 2007. Available at: http://www.avma.org/reference/marketstats/sourcebook.asp. Accessed September 14, 2010.
2. Lascelles BD, Capner CA, Waterman-Pearson AE. Current British attitudes to perioperative analgesia for cats and small mammals. Vet Rec 1999;145:601–4.
3. Capner CA, Lascelles BD, Waterman-Pearson AE. Current British veterinary attitudes to perioperative analgesia for dogs. Vet Rec 1999;145(4):95–9.
4. O'Hagan BJ. Neuropathic pain in a cat post-amputation. Aust Vet J 2006;84(3):83–6.
5. Muir WW 3rd, Wiese AJ, Wittum TE. Prevalence and characteristics of pain in dogs and cats examined as outpatients at a veterinary teaching hospital. J Am Vet Med Assoc 2004;224(9):1459–63.
6. Shaver SL, Robinson NG, Wright BD, et al. A multimodal approach to management of suspected neuropathic pain in a prairie falcon (*Falco mexicanus*). J Avian Med Surg 2009;23(3):209–13.
7. Holton L, Reid J, Scott EM, et al. Development of a behaviour-based scale to measure acute pain in dogs. Vet Rec 2001;148(17):525–31.

8. Murrell JC, Psatha EP, Scott EM, et al. Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. Vet Rec 2008; 162(13):403–8.
9. Roughan JV, Flecknell PA, Orr H. Behavioral assessment of post-operative pain and analgesic effects of carprofen in the domestic rabbit. Abstracts presented at: the World Congress of Veterinary Anesthesia. Knoxville (TN), 17–20 September, 2003. Vet Anaesth Analg 2004;31:282–91.
10. Leach MC, Allweiler S, Richardson C, et al. Behavioural effects of ovariohysterectomy and oral administration of meloxicam in laboratory housed rabbits. Res Vet Sci 2009;87(2):336–47.
11. MeEwen GN Jr. Thermoregulatory responses of restrained versus unrestrained rabbits. Life Sci 1975;17(6):901–5.
12. Holton LL, Scott EM, Nolan AM, et al. Relationship between physiological factors and clinical pain in dogs scored using a numerical rating scale. J Small Anim Pract 1998;39(10):469–74.
13. Arras M, Rettich A, Cinelli P, et al. Assessment of post-laparotomy pain in laboratory mice by telemetric recording of heart rate and heart rate variability. BMC Vet Res 2007;3:16.
14. Rietmann TR, Stauffacher M, Bernasconi P, et al. The association between heart rate, heart rate variability, endocrine and behavioural pain measures in horses suffering from laminitis. J Vet Med A Physiol Pathol Clin Med 2004; 51(5):218–25.
15. Wheat NJ, Cooper DM. A simple method for assessing analgesic requirements and efficacy in rodents. Lab Anim (NY) 2009;38(7):246–7.
16. Shavit Y, Fish G, Wolf G, et al. The effects of perioperative pain management techniques on food consumption and body weight after laparotomy in rats. Anesth Analg 2005;101(4):1112–6 [table of contents].
17. Liles JH, Flecknell PA. The effects of buprenorphine, nalbuphine and butorphanol alone or following halothane anaesthesia on food and water consumption and locomotor movement in rats. Lab Anim 1992;26(3):180–9.
18. Flecknell PA, Morton DB. Use of animals in research. Vet Rec 1991;128(22):531.
19. Farabollini F, Giordano G, Carli G. Tonic pain and social behavior in male rabbits. Behav Brain Res 1988;31(2):169–75.
20. Aloisi AM, Lupo C, Carli G. Effects of formalin-induced pain on exploratory behaviour in rabbits. Neuroreport 1993;4(6):739–42.
21. Gutstein HB, Akil H. Chapter 21. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's the pharmacological basis of therapeutics. 11th edition. New York (NY): McGraw-Hill Companies; 2010. p. 547–90.
22. Stein C, Lang LJ. Peripheral mechanisms of opioid analgesia. Curr Opin Pharmacol 2009;9(1):3–8.
23. Shahbazian A, Heinemann A, Schmidhammer H, et al. Involvement of mu- and kappa-, but not delta-, opioid receptors in the peristaltic motor depression caused by endogenous and exogenous opioids in the guinea-pig intestine. Br J Pharmacol 2002;135(3):741–50.
24. Cosola C, Albrizio M, Guaricci AC, et al. Opioid agonist/antagonist effect of naloxone in modulating rabbit jejunum contractility in vitro. J Physiol Pharmacol 2006;57(3):439–49.
25. Nomura Y, Hayashi S. Pre- and post-synaptic effects of spiradoline and U-50488H, selective kappa opioid receptor agonists, in isolated ileum. Scand J Gastroenterol 1992;27(4):295–302.

26. Dai JL, Ren ZJ, Fu ZM, et al. Electroacupuncture reversed the inhibition of intestinal peristalsis induced by intrathecal injection of morphine in rabbits. Chin Med J (Engl) 1993;106(3):220–4.
27. Flecknell PA, Liles JH. Assessment of the analgesic action of opioid agonist-antagonists in the rabbit. J Assoc Vet Anaesthetics 1990;17:24–9.
28. Portnoy LG, Hustead DR. Pharmacokinetics of butorphanol tartrate in rabbits. Am J Vet Res 1992;53(4):541–3.
29. Shafford HL, Schadt JC. Respiratory and cardiovascular effects of buprenorphine in conscious rabbits. Vet Anaesth Analg 2008;35(4):326–32.
30. Robinson AJ, Muller WJ, Braid AL, et al. The effect of buprenorphine on the course of disease in laboratory rabbits infected with myxoma virus. Lab Anim 1999;33(3):252–7.
31. Barter LS, Kwaitkowski AE. Thermal threshold testing for evaluation of analgesics in rabbits. Paper presented at: Annual Meeting American College of Veterinary Anesthesiologists. Chicago (IL), September 10, 2009.
32. Flecknell PA, John M, Mitchell M, et al. Neuroleptanalgesia in the rabbit. Lab Anim 1983;17(2):104–9.
33. Martinez MA, Murison PJ, Love E. Induction of anaesthesia with either midazolam or propofol in rabbits premedicated with fentanyl/fluanisone. Vet Rec 2009; 164(26):803–6.
34. Foley PL, Henderson AL, Bissonette EA, et al. Evaluation of fentanyl transdermal patches in rabbits: blood concentrations and physiologic response. Comp Med 2001;51(3):239–44.
35. Skarda RT, Tranquilli WJ. Local and regional anesthetic and analgesic techniques: cats. In: Tranquilli WJ, Thurmon JC, Grimm KA, editors. Lumb & Jones' veterinary anesthesia and analgesia. 4th edition. Ames (IA): Blackwell Publishing; 2007. p. 595–603.
36. Greenaway JB, Partlow GD, Gonsholt NL, et al. Anatomy of the lumbosacral spinal cord in rabbits. J Am Anim Hosp Assoc 2001;37(1):27–34.
37. Burke A, Smyth E, FitzGerald GA. Chapter 26. Analgesic-antipyretic and antiinflammatory agents; pharmacotherapy of gout. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's the pharmacological basis of therapeutics. 11th edition. New York (NY): McGraw-Hill Companies; 2010.
38. Turner PV, Chen HC, Taylor WM. Pharmacokinetics of meloxicam in rabbits after single and repeat oral dosing. Comp Med 2006;56(1):63–7.
39. Lichtenberger M, Ko J. Anesthesia and analgesia for small mammals and birds. Vet Clin North Am Exot Anim Pract 2007;10(2):293–315.
40. Doherty MM, Hughes PJ, Korszniak NV, et al. Prolongation of lidocaine-induced epidural anesthesia by medium molecular weight hyaluronic acid formulations: pharmacodynamic and pharmacokinetic studies in the rabbit. Anesth Analg 1995;80(4):740–6.
41. Pypendop BH, Ilkiw JE. Assessment of the hemodynamic effects of lidocaine administered IV in isoflurane-anesthetized cats. Am J Vet Res 2005;66(4):661–8.
42. Taniguchi T, Shibata K, Yamamoto K, et al. Effects of lidocaine administration on hemodynamics and cytokine responses to endotoxemia in rabbits. Crit Care Med 2000;28(3):755–9.
43. Grint NJ, Murison PJ. A comparison of ketamine-midazolam and ketamine-medetomidine combinations for induction of anaesthesia in rabbits. Vet Anaesth Analg 2008;35(2):113–21.
44. Pypendop BH, Verstegen JP. Hemodynamic effects of medetomidine in the dog: a dose titration study. Vet Surg 1998;27(6):612–22.

45. Carter JE, Campbell NB, Posner LP, et al. The hemodynamic effects of medetomidine continuous rate infusions in the dog. Vet Anaesth Analg 2010;37(3):197–206.
46. Suzuki M. Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. Curr Opin Anaesthesiol 2009;22(5):618–22.
47. Holtman JR Jr, Crooks PA, Johnson-Hardy JK, et al. Effects of norketamine enantiomers in rodent models of persistent pain. Pharmacol Biochem Behav 2008;90(4):676–85.
48. Kucuk A, Kadioglu Y, Celebi F. Investigation of the pharmacokinetics and determination of tramadol in rabbit plasma by a high-performance liquid chromatography-diode array detector method using liquid-liquid extraction. J Chromatogr B Analyt Technol Biomed Life Sci 2005;816(1–2):203–8.
49. Souza MJ, Greenacre CB, Cox SK. Pharmacokinetics of orally administered tramadol in domestic rabbits (*Oryctolagus cuniculus*). Am J Vet Res 2008;69(8):979–82.
50. Egger CM, Souza MJ, Greenacre CB, et al. Effect of intravenous administration of tramadol hydrochloride on the minimum alveolar concentration of isoflurane in rabbits. Am J Vet Res 2009;70(8):945–9.